beta-globin gene transfer to human bone marrow for sickle cell disease.

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Public Summary:
Autologous hematopoietic stem cell gene therapy is an approach to treating sickle cell disease (SCD) patients that may result in lower morbidity than allogeneic transplantation. We examined the potential of a lentiviral vector (LV) (CCL-betaAS3-FB) encoding a human hemoglobin (HBB) gene engineered to impede sickle hemoglobin polymerization (HBBAS3) to transduce human BM CD34+ cells from SCD donors and prevent sickling of red blood cells produced by in vitro differentiation. The CCL-betaAS3-FB LV transduced BM CD34+ cells from either healthy or SCD donors at similar levels, based on quantitative PCR and colony-forming unit progenitor analysis. Consistent expression of HBBAS3 mRNA and HbAS3 protein compromised a fourth of the total beta-globin-like transcripts and hemoglobin (Hb) tetramers. Upon deoxygenation, a lower percentage of HBBAS3-transduced red blood cells exhibited sickling compared with mock-transduced cells from sickle donors. Transduced BM CD34+ cells were transplanted into immunodeficient mice, and the human cells recovered after 2-3 months were cultured for erythroid differentiation, which showed levels of HBBAS3 mRNA similar to those seen in the CD34+ cells that were directly differentiated in vitro. These results demonstrate that the CCL-betaAS3-FB LV is capable of efficient transfer and consistent expression of an effective anti-sickling beta-globin gene in human SCD BM CD34+ progenitor cells, improving physiologic parameters of the resulting red blood cells.

Scientific Abstract:
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